Appendectomy During Childhood and Adolescence and the Subsequent Risk of Cancer in Sweden

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ABSTRACT. *Objective.* **Researchers have speculated that surgical excision of lymphoid tissue, such as appendectomy, early in life might confer an increased risk of cancer. In this study, we determined the risks of cancer for people who had appendectomy performed during childhood.**

Methods. **We studied the risk of cancer in a large Swedish cohort of children who had appendectomy performed during the period of 1965–1993. Standardized incidence ratios (SIRs) were computed using age-, gender-, and period-specific incidence rates derived from the entire Swedish population as comparison. Hospital discharge diagnosis data were used to examine cancer risks by categories of surgery, medical conditions, and type of appendicitis. The average length of follow-up was 11.2 years.**

Results. **We found no excess overall cancer risk but noted a significant excess for stomach cancer (SIR: 2.45; 95% confidence interval [CI]: 1.1–4.8) and a borderline increase of non-Hodgkin's lymphoma (NHL; SIR: 1.55; 95% CI: 1.0–2.3). The elevated risks for both cancers were only evident 15 or more years after appendectomy (stomach cancer, SIR: 3.82; 95% CI: 1.7–7.5; NHL, SIR: 2.49; 95% CI: 1.4–4.2).**

Conclusions. **It is reassuring that there was no overall increase of cancer several years after childhood appendectomy. Increased risks for NHL and stomach cancer, occurring 15 or more years after appendectomy, were based on small absolute numbers of excess cancers. As 95% of the subjects were younger than 40 years at exit, this cohort requires continuing follow-up and monitoring.** ***Pediatrics*** **2003;111:1343–1350;** ***childhood appendectomy, appendicitis, Sweden, cancer incidence, cancer risk.***

ABBREVIATIONS. IPR, Inpatient Registry; *ICD, International Classification of Diseases*; *ICD-7, International Classification of Diseases, Seventh Revision*; SIR, standardized incidence ratio; NHL, non-Hodgkin's lymphoma; CI, confidence interval; SES, socioeconomic status.

In 1964, McVay[1] first suggested that appendectomy might predispose to an increased risk of cancer. Subsequently, case-control[2–8] and cohort investigations[9–11] have evaluated associations between appendectomy and selected cancers, but the results were inconsistent. There is little accurate information about long-term cancer risks after appendectomy in childhood. We hypothesized that infections or inflammatory disease leading to appendicitis with subsequent excision of the appendix and immediately surrounding lymphoid tissue at a young age might lead to increased risks of the immune-related malignancies of non-Hodgkin and Hodgkin's lymphoma.[3,11,12] The availability of complete hospitalization data back as far as 1965, linked with nationwide and complete registries for death, migration, and cancer incidence, provided the opportunity for a long-term follow-up investigation of cancer risk in a large cohort of children who underwent appendectomy.

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METHODS

The methods used have been described in detail elsewhere.[13,14] Briefly, the Swedish Inpatient Registry (IPR) was used to identify all patients under age 20 recorded with an appendectomy (Swedish Surgical codes 4510 and 4511) during the time period 1965–1993. The Swedish hospital IPR was established in parts of the country in 1964–1965 and expanded rapidly to cover 75% of the population in 1978 and 100% from 1987. The reporting procedures have been previously described.[13] Each IPR record corresponding to 1 admission contains up to 6 medical diagnosis codes and 6 surgical procedures.[14] Medical conditions listed as discharge diagnoses are coded according to the *International Classification of Diseases* (*ICD*) using the seventh revision (*International Classification of Diseases, Seventh Revision* [*ICD-7*]), for the years 1965–1968, the eighth revision for years 1969–1986, and the ninth revision for 1987–1996. National personal identification numbers assigned to each Swedish resident shortly after birth or immigration were used to link the IPR files with the appropriate registries. All incident cancers diagnosed among children who had undergone appendectomy were ascertained for the years 1965–1993.[15,16]

After linkage to the Swedish Cancer Registry, the hospitalization data were also linked to the Swedish Total Population Registry, the Migration Registry, and the Death Registry to identify IPR records that did not correspond to any living, dead, or emigrated person. These records, for which the National Registration Numbers must have been incorrect, were excluded. The linkages also provided dates of emigration and death, when applicable for all patients in the cohort. Cancers were classified according to anatomic site (*ICD-7*) and morphology.

After completion of all record linkages, which were performed at the National Board of Health and Welfare and Statistics Sweden, the National Registration Numbers were removed from the data set and replaced with individually unique serial numbers that could not be linked back to the subjects. Then the data set was delivered to the Swedish co-authors. No information was elicited directly from subjects, and no subjects or their parents were contacted. All data used in this article were obtained from ongoing computerized registries. The Ethics Committee of the University of Uppsala, Sweden (the previous affiliation of the Swedish co-authors) approved the use of the registry data for this analysis.

Study Population

A total of 111 137 children and adolescents (hereafter referred to as children), under age 20, underwent appendectomy in Sweden during 1965–1993. Excluded from additional consideration were 40 children who died during the same month as the appendectomy and 281 children who received a diagnosis of cancer, designated prevalent cancers, during or before the hospitalization for appendectomy or within the same month as this surgical procedure. These prevalent cancers included 149 (53%) carcinoids of the appendix, 40 brain cancers (mostly astrocytomas), 30 leukemias, and 15 lymphomas. A total of 447 cancers were diagnosed in the cohort beginning 1 month after hospital discharge for appendectomy up through December 31, 1993, including 36 cancers detected during the first year of follow-up. These 36 cancers diagnosed within the first year of follow-up included 11 colon cancers, all of which were carcinoids of the appendix. They were excised at the time of the appendectomy but with their diagnosis mistakenly dated as diagnosed 1 to 2 months after the appendectomy.

Because presence of a subclinical tumor may increase the probability that a child is subjected to appendectomy, selection bias may arise. The first year of follow-up for the entire cohort was excluded. Thus a total of 106 763 patients with 411 detected cancers were included in the subsequent analyses (Table 1).

Categories of Appendectomy and Appendicitis

Only 5.0% of subjects had appendectomy during other surgery (Table 1). Of the remaining 95.0% who had appendectomy alone, a small fraction (0.8%) had appendectomy combined with postoperative drainage.

Medical Diagnosis Categories

Individuals who underwent appendectomy were categorized into 4 groups depending on the medical conditions listed as discharge diagnoses during the corresponding hospitalization during which this surgical procedure was performed. The 4 groups included 1) appendicitis as the only discharge diagnosis ($N = 75\,850$; 71% of the cohort), 2) appendicitis with 1 or more other medical diagnoses ($N = 4025$), 3) no diagnosis of appendicitis but other medical diagnoses were listed on the hospital record ($N = 26\,600$; 25% of the cohort), and 4) no medical discharge diagnosis was provided on the hospital record ($N = 288$; Table 1). For the second and third categories listed immediately above, the other medical diagnoses at the time of appendectomy included congenital malformations (eg, Meckel's diverticulum), hernias, mesenteric lymphadenitis, abdominal colic, infections, gastrointestinal diseases, gynecological diseases, and other health problems.

Although 71% of the cohort had a diagnosis of appendicitis, not all of these diagnoses were acute or perforated appendicitis. Therefore, we also created 3 clinical categories to reflect the extent of appendicitis or other abdominal symptoms, with corresponding *ICD* codes from the seventh, eighth, and ninth revisions shown in the footnote of Table 1. The categories of appendicitis were 1) appendicitis that was perforated with or without abscess, or acute nonperforated (including phlegmonous and gangrenous); 2) mesenteric lymphadenitis with no appendicitis; and 3) various types of appendicitis, some of which were not well defined (eg, appendicitis without peritonitis; chronic appendicitis; appendicitis, not otherwise specified) and other nonappendicitis medical diagnoses such as Meckel's diverticulum, hernias, abdominal colic, infections, gastrointestinal diseases, gynecological diseases, and other health problems. As can be seen in Table 1, the number of subjects with perforated or abscessed appendicitis ($N = 11\,201$ [10.5%]) or acute appendicitis ($N = 68\,382$ [64%]) made up >75% of the

TABLE 1. Swedish Children and Adolescents Who Underwent Appendectomy at Ages <20 During 1965–1993, First Year Follow-up Excluded

Characteristic	*N*	%
Total cohort	106,763	100.0
Males	51,222	48.0
Female	55,541	52.0
Age at appendectomy (y)		
0–4	2,514	2.4
5–9	18,908	17.7
10–14	41,647	39.0
15–19	43,694	40.9
Age at exit (y)		
0–9	1,612	1.5
0–19	26,106	24.5
20–29	49,332	46.2
30–39	24,999	22.9
40–49	5,214	4.9
Surgical procedures		
Appendectomy alone	101,404	95.0
Appendectomy and other surgery	5,359	5.0
Medical diagnosis groupings*		
Appendicitis alone	75,850	71.0
Appendicitis and other diagnoses	4,025	3.8
Other diagnoses, no appendicitis	26,600	24.9
Appendectomy and no medical diagnosis	288	0.3
Appendicitis spectrum†		
Perforated or abscessed appendicitis‡	11,201	10.5
Acute appendicitis (nonperforated)§	68,382	64.1
Mesenteric lymphadenitis	14,757	13.8
Other diagnoses‖	12,423	11.6

* See details in Table 2.

† See details in Table 3.

‡ Perforated or abscessed appendicitis includes appendicitis with abscess or perforation *ICD-7* 55010–55013; *ICD-8* 54000–54003; *ICD-9* 540A, 540B.

§ Acute and nonperforated appendicitis includes types of acute nonperforated appendicitis, including gangrenous appendicitis, *ICD-7* 55000–55003, 55199–55290; *ICD-8* 54090–54208; *ICD-9* 540X, 541, 542.

‖ Other diagnoses includes some appendicitis codes that are not believed to be acute appendicitis, including chronic or recurrent appendicitis, mucocele of the appendix, and other appendiceal conditions and also nonappendicitis codes such as Meckel's diverticulum, hernias, abdominal colic, infections, gastrointestinal diseases, gynecological diseases, and other medical diagnoses.

cohort, mesenteric lymphadenitis almost 14%, and other diagnoses almost 12%.

Evaluation of Infections Before and After Appendectomy

As a possible indicator of whether people who underwent appendectomy had evidence of previous immune dysfunction or, after appendectomy, had an abnormal immune response, we examined hospital diagnoses for infectious disease in each study subject >3 months before appendectomy and hospitalizations that occurred >3 months after appendectomy, until 1 year before cancer or end of follow-up.

Follow-up

Person-years for the cohort were calculated beginning 12 months after the hospital discharge date for appendectomy and continuing until the occurrence of a first primary cancer, death, emigration, or the end of observation (December 31, 1993), whichever occurred first.

Statistical Methods

Standardized incidence ratios (SIRs), the ratio of the observed numbers of cancers to those expected on the basis of age, gender, and calendar year–specific cancer incidence rates for the general population of Sweden, and corresponding 95% confidence intervals were calculated for each cancer category assuming a Poisson distribution. Cancers found incidentally at autopsy were excluded from both the numerator and the denominator rates. The relationship of appendectomy and cancer outcome was evaluated overall and then stratified by gender, age at appendectomy, whether the subject underwent appendectomy alone or with other surgeries, whether the subject had other medical diagnoses (with or without appendicitis), and the time interval (latency) between appendectomy and cancer diagnosis. The χ^2 test for homogeneity was used to assess whether there were statistically significant differences in stratum-specific risks, and the χ trend test for whether there were statistically significant trends by age.[17]

RESULTS

Of the 106 763 pediatric patients available for follow-up (Table 1), there were 51 222 (48.0%) male and 55 541 (52.0%) female patients. The mean age at hospital discharge was 13.6 years (median: 13 years), and the mean calendar year of entry was 1982 (median: 1982). The average length of follow-up was 11.2 years. More than 95% of patients were younger than 40 years at the end of follow-up. A total of 79 875 (74.8%) people had a discharge diagnosis of appendicitis (75 850 with appendicitis only and 4025 with appendicitis and other diagnoses), and 8823 of the 79 875 (11.0%) had perforated appendicitis.

Cancers Occurring After First Year of Follow-up

There was no excess for total cancers (Table 2, column 1) in both genders combined among all children and adolescents who underwent appendectomy at ages 0 to 19 (411 cancers observed vs 410 expected; SIR: 1.00; 95% confidence interval [CI]: 0.9–1.1). No apparent differences in risk were observed between male and female patients (data not shown). Risks were >2.4-fold and significantly increased for total stomach cancers (SIR: 2.45; 95% CI: 1.1–4.8) based on 8 cases, all adenocarcinomas. A 3-fold increase in cancers occurring in the eye was observed (5 cases with different histologic types, SIR: 3.03; 95% CI: 0.98–7.1). Risks were significantly decreased for colon cancer (SIR: 0.42; 95% CI: 0.2–0.9).

TABLE 2. Risk of Cancer Among Children and Adolescents Who Underwent Appendectomy for Appendicitis or in Conjunction With Other Medical Diagnoses in the Absence of Appendicitis, First Year of Follow-up Excluded

Cancers (*ICD-7*)	All Children Who Underwent Appendectomy (*N* = 106 763)			Appendectomy and Appendicitis Only* (*N* = 75 850)			Appendectomy and Other Medical Diagnoses But No Appendicitis (*N* = 26 600)		
	Observations	SIR	95% CI	Observations	SIR	95% CI	Observations	SIR	95% CI
All cancers	411	1.00	0.9–1.1	276	0.97	0.9–1.1	113	1.07	0.9–1.3
Buccal†	11	1.56	0.8–2.8	4	0.80	0.2–2.1	6	3.48	1.3–7.6
Stomach	8	2.45	1.1–4.8	6	2.60	1.0–5.7	2	2.60	0.3–9.4
Colon	7	0.42	0.2–0.9	5	0.44	0.1–1.0	2	0.46	0.1–1.7
Rectum	4	0.99	0.3–2.5	1	0.35	0.0–1.9	2	2.12	0.2–7.7
Lung	2	0.39	0.0–1.4	2	0.55	0.1–2.0	0	0.00	0.0–3.1
Breast	32	0.85	0.6–1.2	20	0.84	0.5–1.3	9	0.79	0.4–1.5
Cervical	35	1.23	0.9–1.7	18	1.01	0.6–1.6	16	1.77	1.0–2.9
Ovary	17	1.17	0.7–1.9	13	1.43	0.8–2.4	2	0.44	0.1–1.6
Testis	41	1.18	0.9–1.6	34	1.25	0.9–1.7	5	0.83	0.3–1.9
Kidney	5	1.24	0.4–2.9	5	1.75	0.6–4.1	0	0.00	0.0–3.8
Bladder	4	0.78	0.2–2.0	2	0.53	0.1–1.9	2	1.80	0.2–6.5
Melanoma	39	0.80	0.6–1.1	25	0.75	0.5–1.1	13	0.99	0.5–1.7
Nonmelanoma	9	1.55	0.7–3.0	6	1.43	0.5–3.1	3	2.29	0.5–6.7
Eye‡	5	3.03	1.0–7.1	2	1.75	0.0–6.3	3	7.15	1.4–20.9
Brain	65	1.22	0.9–1.6	41	1.10	0.8–1.5	19	1.43	0.9–2.2
Thyroid	16	0.88	0.5–1.4	16	0.92	0.5–1.7	4	0.76	0.2–1.9
Bone	8	0.72	0.3–1.4	5	0.63	0.2–1.5	2	0.76	0.1–2.7
Connective tissue	8	0.87	0.4–1.7	7	1.08	0.4–2.2	1	0.43	0.0–2.4
Hematopoietic§	67	1.00	0.8–1.3	54	1.14	0.9–1.5	12	0.74	0.4–1.3
Total lymphoma	50	1.18	0.9–1.6	42	1.39	1.0–1.9	8	0.77	0.3–1.5
Hodgkin's	25	0.96	0.6–1.4	22	1.19	0.8–1.8	3	0.46	0.1–1.3
NHL	25	1.55	1.0–2.3	20	1.73	1.1–2.7	5	1.34	0.4–3.1
Leukemia	16	0.68	0.4–1.1	11	0.66	0.3–1.2	4	0.69	0.2–1.8

* Sole diagnosis of appendicitis, no other medical diagnoses.
† Buccal cancers include 4 tongue, 2 each of mouth and tonsils, and 1 each of parotid, other salivary gland, and pharynx.
‡ Eye cancers includes 2 optic nerve gliomas and 1 each of nonmelanoma of conjunctiva, melanoma of the bulbar area, and mesenchymal sarcoma of the orbit.
§ Hematopoietic includes all lymphoproliferative cancers (lymphomas and leukemias).

Cancer Risks According to Medical Diagnosis

Risk for total hematopoietic cancers was not elevated (SIR: 1.00). For total lymphoma, a modest 39% excess risk was observed among children who underwent appendectomy for appendicitis, but risk was not elevated (SIR: 0.77) among those who underwent appendectomy without appendicitis but with other diagnoses. Risks for Hodgkin's disease were not significantly elevated among either of these 2 major categories of children who underwent appendectomy. A 55% elevated risk for non-Hodgkin's lymphoma (NHL; 25 cases; SIR: 1.55; 95% CI: 1.0–2.3) reflected a significant 73% increase among children who underwent appendectomy with appendicitis and a nonsignificant 34% increase in those who underwent appendectomy without appendicitis. The excess of NHL in both major groups was balanced by a 32% reduced risk for total leukemia (SIR: 0.68; 95% CI: 0.4–1.1).

Cancer risks are shown for children who underwent appendectomy and were discharged with a medical diagnosis of appendicitis alone (Table 2, column 2) and for those who underwent appendectomy with no discharge diagnosis of appendicitis but other medical conditions listed (Table 2, column 3). The overall risk of cancer for patients among whom the appendectomy was accompanied by a diagnosis of appendicitis was not elevated and similar to that of patients who underwent appendectomy with a medical diagnosis other than appendicitis. Cervical cancer was modestly increased overall (SIR: 1.23), but elevated risks were confined to people with other medical diagnoses (SIR: 1.77) and not seen in those with appendicitis only (SIR: 1.01). For patients with cervical cancer, 40% had gynecological discharge diagnoses from hospitalizations before cancer diagnosis. Most were gynecological infections.

Among the 4025 patients with both appendicitis and other diagnoses (data not shown), no cancers were significantly elevated. Total cancer risk was 1.03 (19 cases). Of these 19 cases, there were 4 tumors of the female reproductive organs, 3 breast cancers, and 4 brain tumors. Some cases had gynecologic discharge diagnoses such as ruptured corpus luteum, spontaneous abortion, and acute salpingo-oophoritis. There were also diagnoses of chronic nephritis, acute cystitis, and peritonitis.

Among children who underwent appendectomy and had other medical conditions but no appendicitis, significantly elevated risks were observed for buccal cancer ($N = 6$ including 1 salivary gland, 2 squamous cell, 1 epithelial, 1 mesenchymal, and 1 glandular cell tumor) and eye cancer ($N = 3$, including 2 optic nerve gliomas and 1 melanoma of the bulbar area; see Table 2, column 3).

The overall risk of cancer was elevated only among patients with a diagnosis of mesenteric lymphadenitis at the time of the appendectomy (Table 3). Among the patients with mesenteric lymphadenitis, significantly elevated were buccal cancers (4 cases; SIR: 4.12) and cervical cancer (12 cases; SIR: 2.80). Ten of the 12 cases of cervical cancer had only a diagnosis of mesenteric lymphadenitis at the time of the appendectomy; 1 also had a diagnosis of Meckel's diverticulum, and 1 also had a diagnosis of coxalgia. Among the patients with acute or perforated appendicitis (Table 3, column 1), total hematopoietic cancers were not elevated, but a 32% nonsignificant increase was observed for total lymphoma as a result of a significantly elevated risk of NHL (SIR: 1.63) but no significant excess of Hodgkin's disease (SIR: 1.13). Among patients with other diagnoses (Table 3, column 3), neither total hematopoietic cancers nor lymphoma occurred in excess, but NHL was elevated (SIR: 1.81), as well as eye cancers (SIR: 10.29) and brain cancers (SIR: 2.00). Among the patients with other diagnoses, 440 subjects had a diagnosis of Crohn's disease; only 1 cancer (a melanoma) occurred among patients with Crohn's disease during follow-up.

Cancer Risk by Age at Appendectomy

Risk of cancer by type was evaluated among all children according to age at appendectomy. The risk of all cancers combined was not increased in any of the 5-year age groups (Table 4). No significant patterns of increased risk with age were observed for specific types of cancers. Only 5 cancers (SIR: 0.95; 95% CI: 0.3–2.2) occurred in children who had appendectomy before age 5 ($N = 2514$; data not shown): 1 cancer of the ovary (SIR: 9.36), 1 eye (SIR: 15.63), 2 brain (SIR: 1.62), and 1 acute lymphocytic leukemia (SIR: 1.22). None of these SIRs was statistically significant. Children who underwent appendectomy at ages 5 to 9 had moderately elevated risks of NHL ($n = 6$; SIR: 2.50; 95% CI: 0.9–5.4), and those who had this surgical procedure at ages 10 to 14 ($N = 8$; SIR: 1.45; 95% CI: 0.6–2.9) or ages 15 to 19 ($n = 11$; SIR: 1.40; 95% CI: 0.7–2.5) had modest increases in risk; no cases of NHL occurred in children who underwent appendectomy before age 5. There were no cases of stomach cancer among children who were treated with appendectomy before age 10; 1 case among those who were treated with appendectomy at ages 10 to 14; and a moderate, statistically significant elevation in risk for the 7 cases in those who were treated with appendectomy at ages 15 to 19 (SIR: 3.06; 95% CI: 1.23–6.31).

Cancer Risk by Number of Years of Follow-up

Total cancer risk after hospital discharge was not significantly increased after 1 to 4 years (SIR: 1.03; 95% CI: 0.8–1.3), 5 to 9 years (SIR: 0.90; 95% CI: 0.7–1.1), 10 to 14 years (SIR: 1.11; 95% CI: 0.9–1.3), or 15 to 26 years (SIR: 0.99; 95% CI: 0.8–1.2) of follow-up. The excesses seen for stomach cancer and for NHL were only evident 15 or more years after appendectomy (cancer of the stomach, 8 cases, SIR: 3.82; 95% CI: 1.7–7.5; NHL, 14 cases, SIR: 2.49; 95% CI: 1.4–4.2). Also 15 or more years after surgery, a marked deficit was found for total leukemia (1 case, SIR: 0.20; 95% CI: 0.0–1.1).

Appendectomy Alone Versus Appendectomy With Other Surgeries

Only a small proportion of the cohort had appendectomy with additional surgeries. Few differences

TABLE 3. Risk of Cancer Among Children and Adolescents Who Underwent Appendectomy for Appendicitis According to Type of Appendicitis, First Year of Follow-up Excluded

Cancers (*ICD-7*)	Acute or Perforated Appendicitis (*N* = 79 583)			Mesenteric Lymphadenitis (*N* = 14 757)			Other‡ (*N* = 12 423)		
	Observations	SIR	95% CI	Observations	SIR	95% CI	Observations	SIR	95% CI
Overall	292	0.97	0.9–1.1	68	1.18	0.9–1.5	51	0.98	0.7–1.3
Buccal*	4	0.76	0.2–1.9	4	4.12	1.1–10.6	3	3.68	0.7–10.8
Stomach	6	2.44	0.9–5.3	2	4.86	0.6–17.6	0	0.00	0.0–9.3
Colon	5	1.41	0.1–0.97	1	0.42	0.0–2.3	1	0.48	0.0–2.7
Rectum	2	0.65	0.1–2.4	2	3.96	0.4–14.3	0	0.00	0.0–7.7
Breast	22	0.85	0.5–1.3	3	0.57	0.1–1.7	7	1.06	0.4–2.2
Cervical	19	0.99	0.6–1.6	12	2.80	1.5–4.9	4	0.78	0.2–2.0
Ovary	15	1.53	0.9–2.5	1	0.45	0.0–2.5	1	0.41	0.0–2.3
Testis	35	1.23	0.9–1.7	5	1.26	0.4–2.9	1	0.43	0.0–2.4
Kidney	5	1.65	0.5–3.8	0	0.00	0.0–6.8	0	0.00	0.0–7.9
Bladder	2	0.50	0.1–1.8	1	1.59	0.0–8.9	1	1.90	0.0–10.6
Melanoma	25	0.71	0.5–1.0	9	0.73	0.6–2.5	5	0.75	0.2–1.8
Nonmelanoma	6	1.35	0.5–2.9	3	4.01	0.8–11.7	0	0.00	0.0–6.0
Eye†	2	1.65	0.2–5.9	1	4.16	0.1–23.3	2	10.29	1.2–37.2
Brain	45	1.14	0.8–1.5	8	1.04	0.5–2.1	12	2.00	1.03–3.5
Thyroid	12	0.94	0.5–1.7	3	1.10	0.2–3.2	1	0.37	0.0–2.0
Bone	6	0.71	0.3–1.6	2	1.23	0.1–4.4	0	0.00	0.0–3.4
Connective	7	1.02	0.4–2.1	0	0.00	0.0–2.8	1	0.95	0.0–5.3
Hematopoietic§	55	1.10	0.8–1.4	7	0.73	0.3–1.5	5	0.69	0.2–1.6
Lymphoma	42	1.32	0.95–1.8	4	0.67	0.2–1.7	4	0.86	0.2–2.2
Hodgkin's	22	1.13	0.7–1.7	2	0.53	0.1–1.9	1	0.33	0.0–1.9
NHL	20	1.63	1.00–2.5	2	0.91	0.1–3.3	3	1.81	0.4–5.3
Leukemia	12	0.68	0.4–1.2	3	0.86	0.2–2.5	1	0.40	0.0–2.2

* Buccal cancers include 4 tongue, 2 each of mouth and tonsils, and 1 each of parotid, other salivary gland, and pharynx.
† Eye cancers includes 2 optic nerve gliomas and 1 each of nonmelanoma of conjunctiva, melanoma of the bulbar area, and mesenchymal sarcoma of the orbit.
‡ Cancers occurred in patients with diagnoses on their appendectomy visit such as 27 with abdominal colic, 15 with female reproductive conditions (salpingo-oophoritis, ovarian cysts, tubal sepsis, ruptured corpus luteum, hematoma of corpus luteum, benign ovarian tumor, uterine myoma, acute endometritis), 2 with perforated ulcer, 2 with unspecified appendicitis, 1 infant with anal stricture, and a few children with vague symptoms.
§ Hematopoietic includes all lymphoproliferative cancers (lymphomas and leukemias).

TABLE 4. Risk of Cancer Among Children and Adolescents Who Underwent Appendectomy for Any Reason According to Age* at Appendectomy, First Year of Follow-up Excluded

Cancers	Age 5–9 (*N* = 18 908)			10–14 (*N* = 41 647)			15–19 (*N* = 43 694)		
	Observations	SIR	95% CI	Observations	SIR	95% CI	Observations	SIR	95% CI
Overall	47	1.00	0.7–1.3	125	0.96	0.8–1.1	234	1.03	0.9–1.2
Buccal cancer	4	5.04	1.4–12.9	3	1.29	0.3–3.8	4	1.04	0.3–2.7
Stomach	0	0.00	0.0–19.3	1	1.29	0.0–7.2	7	3.06	1.2–6.3
Colon	1	0.47	0.0–2.6	2	0.35	0.0–1.3	4	0.47	0.1–1.2
Rectum	1	3.91	0.1–21.8	1	0.97	0.0–5.4	2	0.73	0.1–2.6
Lung	1	3.48	0.1–19.4	0	0.00	0.0–3.1	1	0.28	0.0–1.5
Breast	0	0.00	0.0–2.5	5	0.68	0.2–1.6	27	0.94	0.6–1.4
Cervical	1	0.55	0.0–3.1	11	1.50	0.8–2.7	23	1.20	0.8–1.8
Ovary	3	2.33	0.5–6.8	2	0.47	0.1–1.7	11	1.25	0.6–2.2
Testis	6	1.55	0.6–3.4	13	1.03	0.6–1.8	22	1.22	0.8–1.9
Kidney	0	0.00	0.0–8.4	3	2.84	0.6–8.3	2	0.82	0.1–3.0
Bladder	1	2.66	0.0–14.8	0	0.00	0.0–2.6	3	0.91	0.2–2.7
Melanoma	4	0.87	0.2–2.2	11	0.71	0.4–1.3	24	0.84	0.5–1.3
Non-melanoma	2	3.43	0.4–12.4	2	1.07	0.1–3.9	5	1.52	0.5–3.5
Eye	0	0.00	0.0–13.6	2	3.89	0.4–14.1	2	2.49	0.3–9.0
Brain	8	0.89	0.4–1.8	23	1.22	0.8–1.8	32	1.32	0.9–1.9
Hematopoietic†	10	0.90	0.4–1.7	25	1.02	0.7–1.5	31	1.04	0.7–1.5
Lymphoma	7	1.12	0.5–2.3	21	1.34	0.8–2.1	22	1.11	0.7–1.7
Hodgkin's	1	0.26	0.0–1.5	13	1.29	0.7–2.2	11	0.93	0.5–1.7
NHL	6	2.50	0.9–5.4	8	1.45	0.6–2.9	11	1.40	0.7–2.5
Leukemia	3	0.63	0.1–1.8	4	0.46	0.1–1.2	8	0.86	0.4–1.7
ALL	1	0.37	0.0–2.1	2	0.54	0.1–2.0	4	1.72	0.5–4.4
ANLL	1	0.76	0.1–4.2	2	0.64	0.1–2.3	2	0.50	0.1–1.8

ALL indicates acute lymphocytic leukemia; ANLL, acute nonlymphocytic leukemia.
* Five cancers occurred in children who underwent appendectomy before age 5: 1 ovary, 1 eye, 2 brain, and 1 acute lymphocytic leukemia.
† Hematopoietic includes all lymphoproliferative cancers (lymphomas and leukemias).

were observed between those who underwent appendectomy alone and those who underwent appendectomy plus other forms of surgery. Elevated risks for NHL were seen in both groups, but all 8 people who developed stomach cancer had appendectomy alone without other surgeries. Fewer than 5% of

patients who later developed cancer had been hospitalized for other surgeries that removed lymphoid tissue (eg, tonsillectomy; data not shown). For patients who had a history of both appendectomy and tonsillectomy, there was no observed relationship with any specific cancer type, and no patients with both surgeries went on to develop either stomach cancer or NHL.

Infections

Ninety patients of the 411 with cancer (21.9%) diagnosed 12 months or more after appendectomy had hospital discharge diagnoses of infectious disease, with just as many discharge diagnoses of infection during hospitalizations occurring >3 months before appendectomy as those children with discharge diagnoses of infections during hospitalizations occurring >3 months afterward. When we stratified by whether people in the cohort had been hospitalized for previous infection, we found no important differences in the cancer risks between the 2 groups. In fact, all of the cases of NHL and stomach cancer occurred among patients who had no previous hospitalizations for infection before appendectomy (8 cases of stomach cancer, SIR: 2.56; 95% CI: 1.1–5.0; 25 cases of NHL, SIR: 1.67; 95% CI: 1.1–2.5).

DISCUSSION

In concordance with 3 other cohort studies,[9–11] we found no increase in total cancer risk after childhood appendectomy. Data revealed absence of an elevated risk for all cancers combined, whether patients had appendicitis, other medical conditions were present, or additional surgical procedures (other than appendectomy) were performed. Despite the absence of an overall increase in cancers, we found increases of NHL and stomach cancer. In the largest previous cohort study of cancer risk among people who underwent appendectomy (N = 82 157 people of all ages), a modest excess of NHL was reported,[11] whereas previous case-control studies described increased risks in colorectal cancer,[5,7,18] Hodgkin's disease,[5] leukemia,[3] and breast cancer.[5,7] Although previous literature has not been completely consistent, there has been some support for the notion that infectious and inflammatory processes involving the appendix (and possibly other lymphoid tissues) at a young age, perhaps in conjunction with surgery involving these tissues, may be associated with an increased occurrence of lymphoid malignancies.[3,11,12] We found modest support for our hypothesis in that children and adolescents who underwent appendectomy for appendicitis had a small increase in risk of lymphoma (SIR: 1.39) compared with no excess in lymphoma (SIR: 0.77) among those who underwent appendectomy with no appendicitis. The higher risks of buccal cancer and eye cancer among the children who underwent appendectomy without appendicitis were based on small numbers and a diversity of different origins and/or histologies of these cancers. These excesses may have been attributable to chance or multiple comparisons.

Although the pathogenic mechanisms and causative factors involved in appendicitis are not understood, obstructive, infectious, inflammatory, dietary, and genetic factors are thought to be involved.[19–21] Children are more likely to have appendicitis in association with viral, bacterial, and other infections.[22–24] Infectious agents may cause a generalized enteritis/colitis that also involves the appendix, but more often they cause inflammation outside the appendix that may present with symptoms of appendicitis.

We observed a modest excess of NHL, higher among the subset of children who underwent appendectomy with a diagnosis of appendicitis, but this small increase should be considered in light of a modest reduction in risk for the leukemias. The increase in NHL was significantly increased only after a latency period of 15 or more years after surgery, and a corresponding deficit was observed for total leukemia 15 or more years after surgery. Thus, the absence of a dose-response according to latency may indicate that a minimum time period is required for the potentially initiating event (eg, excision of lymphoid tissue with an infected and/or inflamed appendix) to result eventually in the development of a lymphoma after unknown additional lymphomagenic factors or promoters. There are other examples of lymphomagenesis occurring 10 or more years after the initiating event.[25] Our results for NHL are similar to those reported from the cohort study in Denmark,[11] the only other cohort investigation that evaluated risk for NHL subsequent to appendectomy and acute appendicitis. Mellemkjaer et al[11] reported a 20% significant increase among people of all ages who underwent appendectomy for appendicitis. Importantly, a 2-fold higher risk was found among those who underwent appendectomy before age 20. Two case-control studies described conflicting results; one[3] reported an increased risk of lymphoma (based on 7 cases) among those who underwent appendectomy before age 20, and the second[26] found no association of NHL. It may be noteworthy that a small excess risk of Hodgkin's disease was found in a large, population-based cohort of people who underwent tonsillectomy with/without adenoidectomy in Sweden with risk more pronounced among patients who underwent tonsillectomy before age 12,[12] but large case-control studies have not supported this relationship.[27,28] Thus, evidence to date provides some, albeit limited, support that infectious and/or inflammatory disease of lymphoid tissue (including the appendix, tonsils, and adenoids), in conjunction with surgical excision of these tissues at a young age, may increase the risk of subsequent lymphoma. Although we found no evidence of immune dysfunction on the basis of hospitalizations for infections in our cohort, the role that the appendix might play in immunocompetency is unknown.[1,3,29] The appendix is heavily laden with lymphoid tissue that develops during infancy and continues to grow through adolescence and early adulthood.[30] Increasing scientific evidence suggests that the appendix may be an integral component of the large gut-associated lymphoid tissue that has been recently recognized to play an important role in the body's immune system. Experimental findings from rabbit studies have shown

dysfunction of the immune system after neonatal appendectomy.[31]

We found only 2 previous studies reporting on the association between appendectomy and stomach cancer: a case-control study[7] in which a history of appendectomy was more common among stomach, colon, and breast cancer patients than in patients with cerebral hemorrhage and a large Danish population-based cohort study[11] in which a marginally significant elevated risk for stomach cancer was seen in patients who underwent appendectomy for acute appendicitis. No information was reported about age at appendectomy in the case-control study,[7] but >50% of the Danish cohort had appendectomy before age 20. Our study found a >2-fold statistically significant excess risk for stomach cancer overall, with a >3-fold increase at 15 or more years of follow-up. The Danish study reported stomach cancer risk after 10 years of follow-up as still elevated but no longer statistically significant. All but 1 patient in our cohort who developed stomach cancer had their appendectomy performed after age 15. Stomach cancer has been linked with low socioeconomic status (SES) in Sweden and many other populations.[32] Recurrent abdominal pain is also linked to low SES; thus, confounding by SES itself is possible. Current theory supports that *Helicobacter pylori* infection is causally related to the development of stomach cancer.[33] It is believed that *H pylori* is acquired early in childhood and is usually asymptomatic. Some but not all investigators found a link between *H pylori* infection and recurrent episodes of abdominal pain in older children.[34,35] Although *H pylori* was not found in appendiceal tissue in 2 earlier studies,[36,37] it is possible that presence of infection with *H pylori* increases the likelihood of appendectomy, thereby accounting for the increased risk of stomach cancer in our study.

The increased risk of cervical cancer for the subgroup without appendicitis but with other medical diagnoses or mesenteric lymphadenitis may be related to other risk factors for cervical cancer, including human papilloma virus and other gynecological conditions that may occur in conjunction with cervical cancer.

Half of all colon cancers in people younger than 40 years in Sweden occur in the appendix.[13] Because the rates for colon cancer that we used in our calculation included the appendix and the subjects in this study all had appendectomies, if appendicitis itself was not a risk factor for colon cancer, then on the basis of these appendectomies alone, we expected to see a reduced risk of colon cancer in these young subjects. Thus, our findings were totally consistent with what was observed, both in magnitude and in direction.

The strengths of our investigation include the large study population, prospective design, long period of follow-up, no losses to follow-up, and the complete ascertainment of cancer outcome by linkage with a nationwide cancer registry. A unique feature of our study was the comparison of risks according to the presence or absence of other surgical procedures at the time of appendectomy, presence or absence of other medical diagnoses at appendectomy, and the type of appendicitis. The resulting clinically based classification used to stratify by type of appendicitis and appendectomy was more detailed and rigorous than that used in earlier reports.

One limitation of our investigation was the lack of histopathological confirmation of appendicitis and/or other diseases of the appendix. Andersson et al[24] reported a discrepancy of 9% in 2509 examined specimens from appendectomy procedures in Sweden. Among the 219 specimens misclassified, there were 179 (10%) of 1840 false positives and 40 (6%) of 669 false negatives. The net error was an overestimation of appendicitis in 139 (6%) of 2509 cases. Thus, it is likely that the number of patients who had a clinical diagnosis of acute appendicitis in our study would be modestly overestimated. Not all patients with possible appendicitis necessarily undergo surgery, but our study cohort was restricted to those who did. Before 1987, the Swedish hospital database (IPR) included 75% or less of the population; nevertheless, the IPR has been population based since inception and therefore it is difficult to identify any specific bias that could have affected our results. The hospital database included no information regarding the role of other possible confounders such as smoking, medications, and family history of either cancer or appendicitis. Recent reports suggest that smoking in adults and passive smoking in children may be associated with acute appendicitis.[38–40] Unfortunately, we could not examine this issue in our study because of lack of information on parental smoking in the database. Changes in classification over time of the hematopoietic and lymphoproliferative malignancies may have had an impact on the risk estimates for the individual disorders in ways that would be difficult to quantify. The lack of a priori hypotheses about eye and buccal cancer in conjunction with the small number of cases composing these excesses suggest that the increased risks for these rare cancers may reflect chance or multiple comparisons.

CONCLUSIONS

It is reassuring to note that there was no overall increase of cancer in a large cohort of children and adolescents with a long-term follow-up period after appendectomy. Increased risks for NHL and stomach cancer, particularly 15 years or more after appendectomy, were based on small absolute numbers of excess cancers, and 95% of the population were younger than 40 years at exit. This population therefore requires continuing follow-up and monitoring.

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